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DEPARTMENT OF THE ARMY
Fort Detrick
Frederick, Maryland

CHEMILUMINESCENCE OF CYCLIC HYDRAZIDES

During the past few years, increased interest has
been paid to the chemiluminescence of organic compounds.
This was due to the fact that 3-amino-phthalic hydrazide
("Luminol") /1/ /Numbers in brackets refer to similarly num-
bered items in Bibliography at end7 and dimethyl-diacridyl-
nitrate /2/ became known as substances showing intensive
luminescence during oxidizing in an amount which far surpas-
ses all phenomena of chemiluminescence known to that date.
Amino-phthalic haydrazide, in particular (due to its ready
availability in larger quantities), has been more closely
examined by K. GLEU and K. PFANNSTIEL /1/.

Details of preparation and test procedures will not
be given at this point; an extensive table of reference ma-
terial is given in the aforenamed authors' publication. It
was known from the first publication by ALBRECHT /3/ that,
in addition to 3-amino-phthalic hydrazide, phthalic acid
hydrazide (in oxidation with hydrogen peroxyde) will also
yield luminescence, in a somewhat smaller amount than Lumi-
nol, however. Since that time few tests were carried out
which could have served to broaden, on an experimental basis,
our knowledge of luminescent compounds among the hydrazide
group. ALBRECHT had made the observation that luminescence
is a general phenomenon in the oxidation of cyclic hydra-
zides, but did not publish any test result material. Only
WITTE /4/ carried out more extensive test on the luminosity
of various hydrazides during oxidation. He also found that
4-amino-phthalic hydrazide displays the same luminescence

as the 3-amino derivate. My observations in this respect
coincide fully with the results obtained by WITTE. The
question of luminosity in hydrazides of a different struc-
ture, e.g. of the di-p-nitro-benzoic acid hydrazide will al-
so be treated in the following; this subject was broached
by A.A.M. WITTE but no final conclusion reached. Further-
more, we were interested in seeing whether substitution of
the benzol ring into phthalic hydrazide would have any ef-
fect on the latter's luminosity; strong influence had been
noticed by the amino-group in regard to the luminosity of
amino-phthalic hydrazide as compared to the noticeably lower
luminescence in phthalic hydrazide (no satisfactory theore-
tical explanation for this phenomenon has been given, to
date). Moreover, it was intended to find limiting values
for the luminosity of various cyclic hydrazides by examin-
ing not only phthalic acid hydrazide but also compounds of
a simpler structure, e.g. hydrazides of the succinic acid
and the di-methyl-maleinic acid type. Finally, it was in-
tended to include in this investigation compounds substitut-
ing for the nitrogen in the azine-ring.

Effects of Catalysts on Luminescence

In order to permit occasional recording of minimal
intensity of luminescence it had to be possible to stimulate
luminosity of low intensity but relatively long duration, at
least over the period of time required for accurate record-
ing. It had already been reported by ALBRECHT that vigorous
catalytic effects are shown on the hydrogen peroxyde oxida-
tion by blood and potato juice containing peroxydase (enzyme).
Meanwhile, GLEU and PFANNSTIEL have reported extensively on
the intensive luminescence resulting from the addition of
small quantities of hemin in the oxidation of 3-amino-phtha-
lic acid hydrazide by means of hydrogen peroxyde. (I have
been able to observe repeatedly that even hemin in potassium
cyanide solution will still show undiminished effectiveness).
In my examinations I have tried predominantly to use mater-
ial containing peroxydase for purposes of catalysis; my mo-
tivation for this course lay in the hope of thus obtaining
prolonged luminescence even in the case of nearly complete
absence of a catalyst with true catalytic effect. This hope
proved justified: strong intensification of luminescence was
observed when using shredded radish or horseradish (possibly
enriched or concentrated). This luminescence does not quite
reach the intensity level obtained by use of hemin but, on
occasion, showed a duration of up to several days since de-
composition of hydrogen peroxyde is nearly completely absent
when using pure materials. Potatoes showed to be far less

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effective. Catalytic effectiveness varied strongly within several samples of horseradish roots used for these tests, moreover, a strong seasonal change in peroxydase contents appears to prevail. A clear demonstration of this latter fact is given by the varying degrees of luminosity observable in a root of horseradish cut lenthwise and immersed in a rather strong (alkaline-hydrogen peroxyde) solution of amino-phthalic hydrazide, when removing the object of observation from the solution after a short period of immersion: a narrow portion in the cortical layer will be distinctly discernible, showing a much higher degree of luminescence. Brightness of light emitted by several specimen treated in the aforementioned manner was, in fact, of such intensity as to permit easy reading of documents at close range from this light source. The luminosity reaction described in the aforegoing may, occasionally, serve a valuable purpose as an easily applied test reaction for peroxydase contents, in the search for and use of such material. (Boiling of shredded material or juice will completely cancel its catalytic effectiveness, in accordance with the long known instability of peroxydase in higher temperatures). Catalysis of luminescence by means of hemin as well as by peroxydase solutions have proven equally valuable tools in the examination of low intensity luminescence: the aforenamed catalysts, on occasion, yielded results where hydrogen peroxyde in solution of orinated potassa had failed. It should, at his point,

be pointed out that hemin will yield a far higher degree of luminescence in a strong alkaline solution than in a weak one. A further conspicuous observation showed compounds closely related to hemin, containing cobalt or vanadium in their porphyritic complex, to have almost no catalytic effect; this fact permits certain conclusions as to possible biological functions of substances with natural vanadium contents /5/. (HENTZE, H. 213, 125, 1935, in a discussion of the physiological activity of the blood of ascitic patients containing vanadium, also reached the conclusion that vanadium chromogen in all probability does not have a function similar to that of hemin, but rather should be considered an H-donor). In consequence of the fact that osmium tetroxyde (in the oxidation of the bi-acridine derivate), in addition to its marked catalytic properties, also causes an increase in luminescence intensity, a number of active ferric oxides were examined for possible catalytic effects on the luminescence of amino-phthalic hydrazide and bi-acridilic nitrate. (should like to state my indebtedness to Dr. A. TREIBS of the Technical University at Munich, for supplying cobalt and porphyric vanadium complexes and to Prof. FRICKE, Director of the Institute for Anorganic Chemistry at the Technical University at Stuttgart, for furnishing various active ferric oxides for

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these tests). Despite strong general catalytic properties
of these ferric oxides, no specific luminescence catalys:
could be noted, which should be interpreted as a sign fo_
their absolute lack in peroxydatic qualities. On the other
hand, this behavior offers an explanation for the totally
different reaction of amino-phthalic hydrazide toward oxygen
(also in the nascent state and in the activated form offered
by peroxydase and hemin). The sensitivity of amino-phthalic
hydrazide to any active form of oxygen (even when not sup-
plied in the form of hydrogen peroxyde) is shown by the
starting of luminescence in an alkaline solution of Luminol
(in low concentration) upon passage of supersonic waves. The
characteristic luminescent patterns formed during the pass-
age of such waves will cease immediately upon interruption
of the latter, i.e. they are not caused by the hydrogen per-
oxyde itself. These tests were carried out in the Institute
for Electrochemical Physics (Director Prof. GRUBE), under the
assistance of Dr. G. SCHMIDT who will report on these tests
in another publication.

Effect of Substitution of the Benzol Ring
in Phthalic Hydrazide

Since the amino group causing the strong luminescence
in Luminol is chemically characterized by easy oxidizability,
a number of phthalic hydrazides were manufactured which con-
tained a similarly easily oxidizable group in place of the
amino group. Importance of oxidizability in the substituted
group (in certain instances) is demonstrated by the fact that
the hydrazino-phthalic hydrazide derived from the amino-phth-
alic hydrazide yields a stronger luminescence (with H_2O_2) than
amino-phthalic hydrazide proper. It should be noted, however,
that only a negligible increase in luminescence is caused by
the adding of hemin. We conclude from observations that a
diazonium salt of amino-phthalic hydrazide must have partic-
ularly high oxidation sensitivity. This compound (with H_2O_2)
produces a luminescence of such brilliance as has not yet
been reached by any other substance and is comparable only
to the best type of luminescence obtained from Luminol, util-
izing hemin. Hemin addition to this diazonium salt also has
no influence on the luminescence, which is only of short dur-
ation.

A conspicuous fact is shown by di-amino-phthalic hy-
drazide (even when used not in its pure form but in compound
containing considerable quantities of this substance): des-
pite easy oxidizability it will yield not nearly so intensive
a luminosity as mono-amino-phthalic hydrazide. Only in its
relatively high sensitivity even in highly diluted solutions

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does this compound show a similarity to the mono-amino derivate. Luminescence is still very much weaker in the di-amino-pyromellithic acid-di-hydrazide; this substance yields hardly any luminescence and demonstrates the importance of the overall arrangement of a substance .. its chemiluminescence. The effect of the substitution of an amino-group in luminol was shown by GLEU and PFANNSTIEL by manufacturing N-methyl-3-amino-phthalic hydrazide which emitted almost as bright a luminescence as the methyl free base. Another compound manufactured by myself (the benzal compound of hydrazino-phthalic hydrazide), however, displayed noticeably reduced luminosity; a certain part of this luminescence is even caused by components of the free hydrazine compound resulting from dissociation of the latter.

Since aniline shows a certain similarity (in regard to oxidizability) to phenol, 3-oxi-phthalic hydrazide was also manufactured and tested. In this case, too, introduction of the oxi-group resulted in stronger luminescence as compared to phthalic hydrazide which, however, does not reach the degree of intensity observable in Luminol. 3,6-dioxi-phthalic hydrazide has shown even lower luminous properties, despite its high oxidizability rate as a hydroquinine derivate: in alkaline solution it discolors rapidly upon contact with air. Luminescence emitted by all these compounds has a bluish hue, similar to that of Luminol. A comparison of the color emitted by all the various hydrazides examined (in so far as color could be determined at all in the case of very faint emission) showed that only one compound emitted luminescence of a somewhat different color: the quinoxaline-2,3-di-carboxylic acid hydrazide which shows luminescence of a more greenish-yellow color. Accurate observation is impeded by the low solubility of alkali salts which, in addition, will produce solutions of a brownish-red color.

Hydrazides of polycyclic ring systems (/6/ anthraquinone-2,3-di-carboxylic acid hydrazide was manufactured and tested as a sample of this group) show a dintinctly lower degree of luminescence, as compared to phthalic acid hydrazide. The fact that the saturated character of the azine ring will have no detrimental effects on the reaction proper is evidenced by the luminescence of succinic acid (not obtained in pure form). This example also shows that no further ring need be attached to the azine ring in order to produce luminescence. This means that luminescence will have to be expected for oxidation of di-methyl-maleinic acid hydrazide; this expectation has been proven correct by our tests. Luminescence was also displayed by a quadruple ring of di-methyl-malonic acid hydrazide. For a completion of

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this group of tests we shou   like to list pyridine-2,3-di-
carboxylic acid hydrazide, with an intensity in the order of
magnitude of phthalic acid hydrazide. (The following was
ins   ed during proof reading of this article:) K. GLEU and
M. ....RNAGEL (this journal, (2) 148,72 (1937)) have mean-
while manufactured quinolinic acid hydrazide (and related
compounds) without having been able to observe luminescence.
Identity of the compound is established by its melting point,
although no exact analysis of this compound could be obtain-
ed.

       All these compounds (manufacturing directions for
whi~ are given --- where required -- in the chapter describ-
i   ..st cedures) without exception show luminescence dur-
i., alkaline oxidation. In view of the theory of lumines-
cence propounded by H. O. ALBRECHT it became of particular
interest to examine whether luminescence would be observable
in hydrazides where substitutions had been made in the ni-
trogen of the azine ring.

Reaction Diagram According to Albrecht
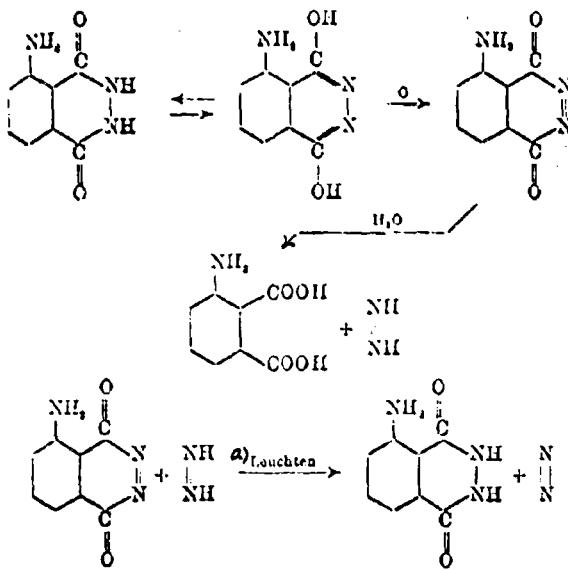
/Legend:7 a) Luminescence.

       This question has, meanwhile, also been examined by
K. GLEU and PFANNSTIEL resulting in their observation of

absence of luminescence in 3-methyl-amino-phthalic acid hy-
drazide which is further methylized at a thus far unknown
position in the azine ring. These authors have, consequent-
ly, arrived at the conclusion that the occurrence of lumi- :-
cence presupposes that no substitution has taken place in
the (radical) hydrazine residual part. I had also been in-
vestigating this question for quite a time and had been hop-
ing to arrive at a clear and final decision through my tests
conducted on other derivates. Although such a decisive
statement is not yet possible I will, at this point, report
on my tests since, thus far, conclusions reached on the bas-
is of my test results are contrary to those reached by GLEU
and PFANNSTIEL and final clarification of this issue may
have a certain bearing on research conducted in the area of
chemiluminescence.

Through double decomposition of the easily manufac-
tured silver salt of (nitro-) phthalic hydrazide by means of
benzyl chloride I obtained benzyl derivates of the former
compound. In this reaction the benzyl group has entered in-
to the molecule in an ether type bond (L), as evidenced by
the overall chemical characteristics. (This bond will dis-
sociate in concentrated hydrochloric acid: benzyl chlorid
will pass out when this solution is boiled). The O-methyl
derivate of phthalic acid hydrazide had previously been manu-
factured by F. M. ROWE and A. T. PETERS /7/ also using the
approach via the silver salts. The ether type nature of
the benzyl group bond in the phthalic acid hydrazide is fur-
ther illuminated by the method of manufacturing the isomeric
compound where benzyl is bonded to the nitrogen of the hydra-
zine group. The latter compound is obtained by means of re-
action of the phthalic acid anhydride with benzyl hydrazine
(II).
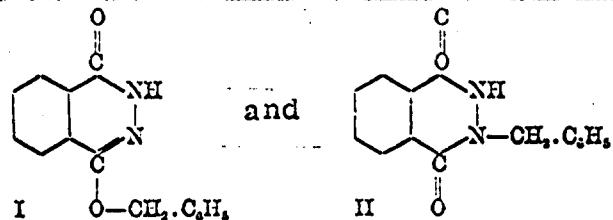
(The manner of notation used here is not intended to
be indicative of possibly existing enol forms of this com-
pound).

The O-benzyl compound proved to possess adequate lum-
inous qualities during oxidation, but even the N-benzyl type

compound showed distinctive light emission when oxidized. Very similar phenomena were found in the derivatives of nitro-phthalic acid hydrazide, except that this substance showed even stronger luminescence after reduction to the amino-group. The very last example, however, leads to doubts in so far as there is a possibility (during catalytic and Sn-hydrochloric acid reduction) of traces of the benzyl group bonded to the nitrogen having been split off, which fact is absolutely reconcilable with the reaction capabilities of the benzyl group. Even more caution is indicated in the case of the O-benzyl compounds: incomplete double decomposition of the silver salts may already account for the presence of traces of phthalic hydrazide, despite the use of alkaline solution (in which only the non-substituted phthalic hydrazide would be well soluble) for the rinsing of the reaction products. I used benzyl hydrazine as the basic product for the manufacture of N-benzyl-phthalic hydrazide; removal of hydrazine was possible only through repeated distillation. In view of the extreme sensitivity of the luminescence reaction even repeated recrystallization of the early crystallizing N-benzyl phthalic hydrazide must be considered insufficient to meet the degree of purity required (in particular since phthalic hydrazide offers much more difficulty in regard to solubility). Even when extreme purity may have been attained in N-benzyl-phthalic hydrazide, luminescence resulting from oxidation would remain a probability if we bear in mind the ease with which the benzyl rest (attached to the nitrogen atom) will dissociate; WEGLER and W. FRANK /7a/ have been able to demonstrate this in various tertiary benzyl amines through oxidation with nitrous acid.

For these reasons I have attempted to produce hydrazides with such substitutions that at no place during synthesis there could have been a possibility of hydrazine entering into the compound or any such easily freed residual groups (e.g. benzyl) being present. I have, for example, tried to obtain nitro-phthalic acid-phenyl hydrazide by using another approach than the one taken by GLEU and PFANNSTIEL /7b/ (who very probably had already manufactured this substance); chemical constitution of this compound has, however, not yet been formulated. Through direct double decomposition of nitro-phthalic-acid with phenyl hydrazine at 210° Celsius I obtained derivates which were soluble in alkaline solution. These derivates, in other words, constituted either an acid hydrzide (1 and 1a) or the hydrazides desired (2 and 2a), but never the phthalimide type shown by formula 3. After reduction with zinc in glacial acetic acid (methanecarboxylic acid) + hydrochloric acid, however, derivates

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were obtained which proved practically unsoluble in alkaline solutions; we may suppose that a composition of the two forms 2 and 2a has been formed.
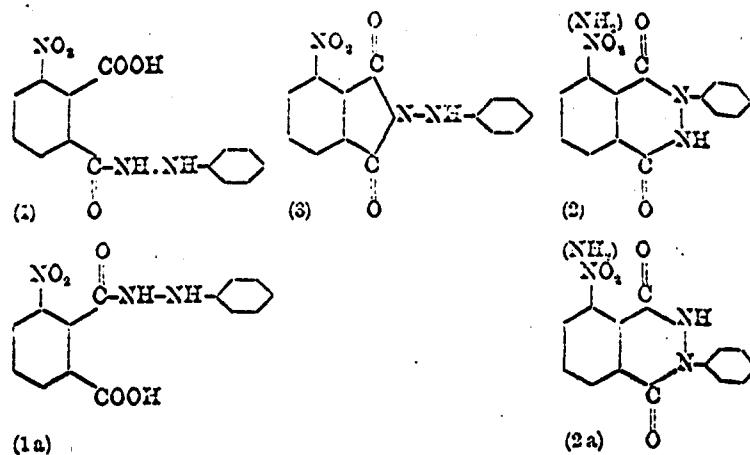
These compounds also show distinct luminescence during oxidation with hydrogen or hemin. Luminosity in a sample is, however, reduced to a fraction of its original value when the substance is purified repeatedly by means of precipitation (with acid) from a base diluted with alcohol-water solution. It is, moreover, possible that the two isomeric forms 2 and 2a show basic differences in their luminescence characteristics. The probable presence of two isomeric forms is further indicated by the very variable and not clearly defined melting point of 216° to 270° Celsius. GLEU showed a melting point of 220° Celsius for his hydrazide (obtained by another method) and BOGERT /8/ 285° for a hydrazide obtained by a third method. Separation into two different pure derivates has not been possible. The tests do, however, from a basis for the assumption that certain phthalic hydrazides substituted at the nitrogen atom may show chemiluminescence. Another attempt will be made to solve the questions inherent in this problem, which will be based on larger quantities of test materials and will use different reaction approaches and methods. This publication will not consider the problem of luminescence in open hydrazides investigated previously by WITTE (e.g. di-o-amino-benzoic acid hydrazide), although I have been able to observe faint luminescence in these compounds, also. In view of the extreme sensitivity to possibly present traces of nitro-or- amino-phthalic acid and their hydrazides this is another case where only a very profound experimental investigation will yield final and decisive results.

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Addendum: I have meanwhile also tried the method given by BOGERT for the manufacture of amino-phthalic acid phenyle hydrazide. By heating 3-amino-phthalimide for several hours with phenyle hydrazine (to 210° C) I obtained a yellow product. It was possible to recrystallize this substance from diluted alcohol but even after repeated re-crystallization it did not show a sharply defined melting point (285° C), as given by BOGERT. I did not succeed in purifying this substance so as to obtain a product with uniform characteristics. It is conspicuous that the various mother liquors, as well as the final product (with hydrogen peroxyde and addition of hemin) produced distinctly observable luminescence for a short time.

The table given in the following is intended to provide a survey of the degree of dilution at which various hydrazides will still show luminescence when oxidized with H_2O_2 and catalyzed with peroxydase or hemin. The concentrations shown do not represent the lowest degree of dilution obtainable since observations were carried out with normal fatigue conditions prevailing in the observers' eyes. High sensitivity is conspicuous in Luminol which, under the test methods used, reaches that of bi-acridylium salt. Identical to observations made for this salt slight luminescence was noted in Luminol (in strong alkaline solution) upon slight heating.

Survey of Chemiluminescence in Some Hydrazides

Compound	Maximal dilution at which luminescence was still observable
Phenazine	No emission
Phthalazine	" "
Phthalazone	" "
Phthalic hydrazide	2×10^{-6} g/ccm
4-bromo phthalic hydrazide	5×10^{-7} " (grams/ cubic centimeter)
Pyridine-2,3-dicarboxylic acid hydrazide	5×10^{-6} "
Diethyl-maleinic acid hydrazide	6×10^{-6} "
Diethyl-malonic acid hydrazide	4×10^{-6} "
3-amino phthalic acid hydrazide	1×10^{-10} " (t=35° C) 2×10^{-7} " (still very bright)

Hydrazino-phthalic acid hydrazide	3×10^{-7} "
3,5-diamino-phthalic acid hydrazide	2×10^{-9} "
3-oxy-phthalic acid hydrazide	2×10^{-9} (brighter than diamino compounds)
3,6-dioxy-phthalic acid hydrazide	2×10^{-6} g/ccm
N,N'-dibenzyl-phthalic acid hydrazide	No emission
3-amino-phthalic acid benzyl hydrazide	$3 \times 10^{-}$ g/ccm

Description of Tests

3-amino phthalic acid hydrazide (Luminol)

Manufacture was done in accordance with the method given by E. H. KUNDRESS /12/, except that (for the purpose of obtaining the highest possible degree of purity) reduction of the nitro group was not effected by means of hydrogen sulphide, since the latter agent frequently introduces sulphuric traces which are difficult to remove. Instead, hydrogenation was effected by means of Pd-animal charcoal in alkaline solution. Subsequent reduction proves easy and produces a total yield.

3-hydrazino-phthalic acid hydrazide

Diazotization of 3-amino phthalic acid hydrazide. 4.5 g of Luminol will be dissolved in diluted warm soda lye (slight excess) then 1.9 g of sodium nitrite are added and the resulting solution is cautiously poured into excessive 10% hydrochloric acid (at -2°C), under constant stirring. If diazotization is performed slowly, at the prescribed temperature (may rise to $+5^\circ$C) a perfectly clear slightly yellowish solution of the diazonium salt will be obtained. If the Luminol-sodium nitrite solution is poured into the hydrochloric acid too quickly or under inadequate stirring, darker solutions will result which in most cases will contain small parts od diazo-amino compound. This diazo-solution is stable over a longer period of time at 0° Celsius. Poured into soda lye, a nearly colorless solution will form (via darker intermediary stages) which combine easily with phenols and naphthols.

The alkaline solution of this diazonium salt emits light of extraordinary brilliance with hydrogen peroxyde,

probably surpassing even the luminescence intensity of Luminol obtained by addition of hydrogen peroxyde and hemin to the latter. Diazo-luminescence is, however, only of short duration.

Reduction to hydrazine. Hydrochloric acid is introduced into the hydrochloric solution of the diazonium salt at -8°C; this solution is combined (in small batches at a time) with stannous chloride (30% excess). Temperature increase over 0°C must be avoided in this process. After approximately 2 hours a crystalline sediment will have formed, consisting of the hydrochloride of the hydrazine formed in this process. For the purpose of removing the stannous salt adhering to the compound the hydrochloride will be dissolved in 1% hydrochloric acid. The hydrazine hydrochloride will be precipitated again by introducing hydrochloric acid at sub-zero temperature. The yield in hydrazine hydrochloride is nearly 100%. The light yellow hydrazine is separated form the hydrochloride by means of diluted lye solution. Hydrazine, like Luminol is soluble in alkaline solution, but shows a far stronger luminous effect than Luminol, upon addition of hydrogen peroxyde; addition of hemin as a catalyst on the other hand, does not produce, as in the case of Luminol, a marked increase in luminescence intensity. No increase in this intensity could be effected. The uncombined base will melt (with unclear melting point between 280 and 300° Celsius) under gas generation and decomposition.

From hydrazine hydrochloride and benzoic aldehyde, with addition of the computed quantity of alkaline solution (in alcohol) a benzal compound (melting point 310 to 312°C) may be obtained. Luminescence in this compound is lower, under any test conditions, than that of hydrazide or Luminol.

3.772 mg substance: 0.636 ccm N(21°C, 754 mm pressure)
Benzal compound $C_{15}H_{12}O_2N_4$ computed N 20.00 Found N 19.43

Benzoic aldehyde is easily separated again by addition of alkaline solution.

3-oxyphthalic acid hydrazide. All hydrazides were manufactured in the manner stated for Luminol, unless otherwise noted.

3-oxyphthalic acid. This acid has been previously manufactured on various occasions by saponification of 3-methoxy phthalic acid /13/ or by boiling of the diazonium salt of 3-amino phthalic acid /14/. The latter method, based on the easily obtainable 3-nitro phthalic acid, appears to offer the most expeditious approach. We have

abstained from isolating the amino phthalic acid which would have offered numerous difficulties, since accurate observation of the formation of amino phthalic acid (through catalytic reduction of 3-nitro phthalic acid in alkaline solution) has been possible. Reduction occurs very rapidly and completely when using Pd-animal-charcoal.

Diazotization. The alkaline solution of the amino phthalic acid was given a strong admixture of sulphuric acid and was subjected to the diazotization process at +7° Celsius. The diazonium salt is hardly soluble in water (in cold temperatures) and precipitates nearly completely. (It offers a convenient way for purification of the amino phthalic acid. Caution is indicated: at 50 to 60°C combustion will occur, in the dry state!). The diazonium salt, after precipitation will be dissolved in sufficient quantity of water, under very slight heating. At a temperature of 30 to 40°C nitrogen generation will terminate after approximately $\frac{1}{2}$ hour. This fact should best be verified by using the combinability of diazonium salt with chromotropic acid in alkaline solution. By means of the ether extraction method a brown crystalline substance will be obtained, which had been recrystallized from benzol with slight additions of alcohol and acetone. This acid proved to have the unclearly defined melting point (as previously found by REMSEN and STOKES [15]), lying between 150 and 152° Celsius. It is unsoluble in benzol, chloroform, petroleum ether; well soluble in ether, alcohol, ethyl acetate (acetic ether), acetone and water. The hydrazine contained in the hydrazine sulfate was recrystallized from an acetone-alcohol solution (9:1) and showed a melting point with strong decomposition at 300° Celsius. This hydrazide displays good solubility in alkaline solution and shows similar but much weaker luminescence as Luminol.

3.089 mg substance :).406 ccm N (21° Celsius, 754 mm pressure)

$C_3H_5O_3N_2$ Computed N = 15.73   Found N = 15.10(?)

This compound shows great obstinacy in its retention of a small quantity of acid hydrazide. Since this small trace was of no particular interest or importance (since no increase of luminescence could be effected) no further purification was attempted.

3.5-diamino phthalic acid hydrazide

3,5-dinitro phthalic acid was produced in accordance with the method stated by EDER and WIDMER [16]: nitration

of o-toluylic acid to form the dinitro compound, saponification and subsequent oxidation of the methyl to carboxyl, by means of diluted nitric acid in the bomb tube. EDNER and WITMER have pointed out that the previously used oxidation temperature of 190° Celsius had inevitably led to complete destruction of the bomb tubes, due to complete oxidation or formation of dinitro-benzoic acid. This fact I can verify and supplement: when this acid was subjected to oxidation (according to EDER and WITTMER'S instructions) in the V_2A autoclave, a reasonably good yield of dinitro phthalic acid was obtained in one case but concurrent formation of dinitro benzoic acid had taken place, as indicated by the high pressure readings.

In a new attempt, using freshly manufactured dinitro toluylic acid, only dinito benzoic acid could be obtained, despite an even further reduction of the oxidation temperature and various changes made in regard to other conditions. Even at temperatures of 150 to 160° Celsius the ratio of dinitro benzoic acid produced was so large that hardly any dinitro phthalic acid was obtained, aside from the remaining dinitro toluylic acid which had not yet participated in the reaction. The reason toluylic acid which had not yet participated in the reaction. The reason for the easy separation of CO_2 had, therefore, to be sought in another factor and was, tentatively, ascribed to the sulphuric acid adhering to the crude acid from the nitration process. It was subsequently verified that dinitro toluylic acid recr   alized from a watery alcohol solution in the nitric acid oxidation process immediately showed an excellent yield in dinitro phthalic acid; when purest dinitro toluylic acid was used no mentionable CO_2 generation was observed, with oxidation temperatures held below 170° Celsius. Oxidation based on pure acid was thus performed with good results, at temperatures of 156 to 165° Celsius and a duration of 5 to 6 hours. The anhydride may be obtained from the acid by using the well known method of boiling the substance with a 5-fold excess in acetic acid anhydride and precipitation with benzol.

Formation of hydrazide. 12 grams of anhydride will be floated on approximately 15 ccm alcohol and will be mixed (in small batches) with 2.65 (instead of 2.5) grams of hydrazine hydrate. The alcohol will be slowly distilled off and the remaining substance heated to nearly 200° C for appr. 3 hours. The brown crystalline substance resulting from this process will be dissolved in diluted alkaline solution and filtered to remove a small portion of possibly remaining foreign matter. A small amount of acetic acid is added to the

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brown solution which will result in the formation of brown
smears. These latter will be brought to an easily filterable
state by heating for 3 hours on the water bath. Hydrochlor-
ic acid is then added to the filtered substance, resulting
in finely granulated crystalline precipitation. The result-
ing substance shows a melting point of 300°C and decomposi-
tion at this temperature. A sample treated with hot acetic
acid had a melting point of 303 to 307°C. The compound is
soluble in alkaline solution, showing a brown color. The
same compound precipitates with various mineral acids, which
excludes salt formation. Treated with benzoic aldehyde (in
excess), no indication was found for a forming of a benzal
compound which may have originated from the acid form (III)
or the isomeric form (II). Solubility of the compound in
water leaves room for the suspicion that the acid hydrazide
(III) has been obtained. Presence of the other type is ex-
cluded by this compounds solubility in alkaline solution.
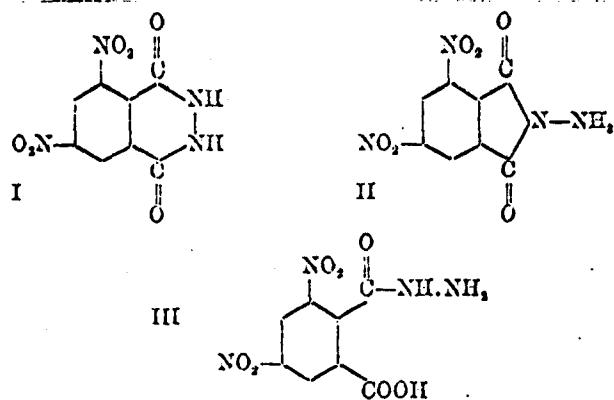
2.699 mg substance: 0.518 ccm N (24° Celsius, 754 mm pres-
   sure)
   $C_3H_4O_6N_4$ Computed for I or II   N = 22.22   Found N = 22.4
        $C_3H_6O_7N_4$ Computed for III   N = 20.74

     Analysis justifies the assumption that pure dinitro
phthalic hydrazide was obtained (form I). Solubility in hot
water may be explained by strong enolization of the hydrazide.

     Hydration. 2 grams of hydrazide were reduced in
methanol, using Pd-animal charcoal as a catalyst. Hydration
occurs very rapidly, using nearly the exact quantity of hydro-
gen computed. A white product was obtained which showed good
solubility in alcohol as well as in alkaline solution.

     Slight luminescence was observed with hydrogen perox-
yde as well as with chloride of lime, during the oxidation

proces.. ..is luminescence, however, showed nearly equal
intensity even in very strongly diluted solutions.

3.130 mg substance: 0.739 ccm N (24° Celsius, 758 mm pres-
    sure)

 $C_8H_6O_2N_4$ Computed N 25.76   Found N 27.1(?)

Pyridine-2,3-dicarboxylic acid hydrazide. Obtained
in the usual manner from dicarboxylic acid. Soluble in di-
luted hydrochloric acid and alkaline solution. Dissolve in
ammonia, remove excess ammonia by heating, add diluted hydro-
chloric acid to the point where solution shows sour charac-
ter and immediately add 1/3 vol ethyl alcohol. White powder
will settle after trituation. Melting point 209° C. Luminos-
is shown with hydrogen peroxyde, similar to the phthalic acid
hydrazide.

3.268 mg substance: 0.724 ccm N (23° Celsius, 754 mm pres-
    sure)

    $C_7H_6O_2N_3$ Computed N = 25.76   Found N = 25.35

2,3-quinoxaline-carboxylic acid hydrazide. Quinoxa-
line dicarboxylic acid was used as the base substance in this
test and was manufactured according to HIRNBERG and KOENIG
/17/ from phenylene diamine and dioxy tartaric acid. The an-
hydride is obtained from this compound (according to PHILIPS
/18/) by using the 10-fold quantity of acetic acid anhydride.
The melting and decomposition point of 251° C was found to be
incorrect since this anhydride will already decompose at
242° C and complete melting will only take place at 276° C.
The anhydride dissolved readily in cold water under regenera-
tion of acid. The hydrazide was extracted from the anhydride
in alcoholic solution with addition of hydrazine and subse-
quent heating to 200° C for two hours. It will dissolve in
lye solution with a violet reddish color. The sodium salt
will be precipitated by means of concentrated soda lye. The
free hydrazide is precipitated (for purification purposes)
from the boiling, slightly alkaline solution with hydrochlor-
ic acid. After repeated purification a light yellow crystal-
line powder was obtained which did not melt at temperatures
below 330° C. Luminescence could be observed after addition
of soda lye or chloride of lime, showing a more yellow-green-
ish hue than the other phthalic hydrazide derivates tested.
Apparently this compound still contains open sour hydrazide
as indicated by the analysis which showed only 25.24% N, in-
stead of 26.17% computed (while sour hydrazine would show
24.3% N).

<u>4,6-dioxy phthalic acid hydrazide.</u> The required dioxy phthalic acid is manufactured according to the method given by THIELE and GUENTHER /19/. The easiest way of purification is offered by re-crystallization from acetone. The reaction path is shown by the following equation:
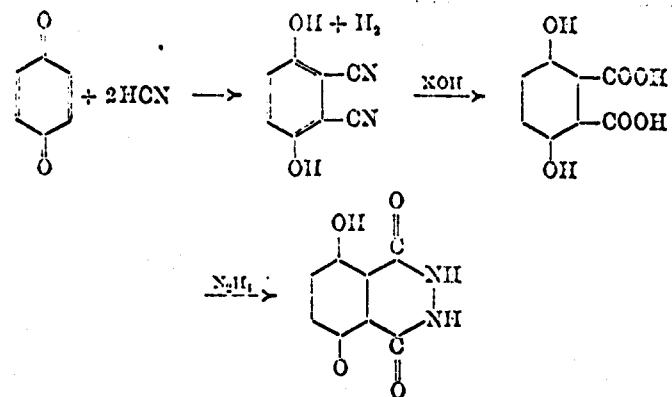
The following approach may be used to produce the desired hydrazide: 4 g of the acid will be combined with a small quantity of alcohol and 2.6 g of hydrazine sulphate and 4 g of sodium acetate, dissolved in 50 to 60 ccm of water will be added to the previous solution. All liquid will be vaporized (under constant stirring) until a completely dry product is obtained. The latter is again dissolved in water and the drying process cautiously repeated over an open flame. The resulting powder will be heated in an oil bath at 165°C for 4 to 5 hours. The reaction product is then boiled twice with diluted hydrochloric acid and filtered. The substance retained by the filter will dissolve readily in diluted alkaline solution, showing a light brown color. An even better approach yielding this hydrazine leads via the dioxy-phthalic acid anhydride which will form if the basic acid is boiled for a short time with the 15-fold quantity of acetic acid anhydride. The desired anhydride will crystallize in the form of needles during the cooling process and will show a melting point of 153°C. When this anhydride is heated with an excess (30%) of hydrazine hydrate and a small amount of alcohol, then evaporated until dry state is reached and heated, for 3 more hours, to 225°C, the hydrazine will be obtained in usable quantity and in a purer form than that offered by the first quoted manner of production. Purification is effected by dissolving in alkaline solution (1 g of hydrazide in 50 ccm of 1% sodium lye), diluted with alcohol to 5 times the original volume and soured (under stirring) with acetic acid. Hydrazine will precipitate in crystalline form

after a short period. The needles are of a very light yellow color and will not melt at temperatures below 340°C. The hydrazide will dissolve in alkaline solution with magnificent fluorescence, similar to that of Fluoresceine (red-yellow greenish). Only slight luminescence is produced by addition of hydrogen peroxyde which is slightly increased by addition of chlorine of lime solution.

4.700 mg substance: 8.540 mg CO_2;   1.310 mg H_2O
3.188 mg substance: 0.401 ccm N (23° Celsius, 763 mm pressure)

$C_8H_6O_4N_2$ Computed: C=49.48(%) H=3.09(%) N=14.44(%)
                Found: C=49.59   H=3.11   N=14.7

Diamino-pyro mellithic acid hydrazide. The compound was produced in the manner indicated by the formulae given in the following. Detailed information concerning working procedures will, in this publication, only be given in such cases which indicate a departure from procedures stated in the respective reference literature.

Acetyl trimethylbenzene. 240 g of trimethylbenzene produced by Schering-Kahlbaum will be mixed with 300 g of pulverized aluminum chloride and 1300 ccm of carbon disulphide. 170 g (theoretically 156 g) of acetyl chloride are added (in small quantities at a time), under frequent shaking of the mixture. The main reaction, which should be permitted to take place at room temperature, will be completed after approximately 20 minutes. The substance should subsequently be heated in a water bath and the reaction compound be kept at the boiling point for approximate $\frac{1}{2}$ hour. Yield: 209 mg ketone with a boiling point of 128 to 132 C° at 14 mm.

Durylic acid. Oxidation is effected readily with the method stated by MILLS [21]. For purification of the resulting acid I have used the method of recrystallization from acetone which yielded 53% of pure acid. The remainder consists of a mixture of isomeric acids, in consequence of the use of the factory produced trimethylbenzene.

CH$_3$ / CH$_3$ a) Pseudokumol —CH$_3$COCl / AlCl$_3$→ CH$_3$ / CH$_3$ —COCH$_3$ — 20) NaOBr → CH$_3$ / CH$_3$ —COOH — 21)

CH$_3$ / CH$_3$ / COOH —HNO$_3$→ NO$_2$ / CH$_3$ / CH$_3$ / COOH / NO$_2$ — 22) —KMnO$_4$→ NO$_2$ / COOH / COOH / COOH / COOH / NO$_2$ — 22)

b) Dinitro-durylsäure   c) Dinitro-pyromellithsäure

—2+N$_2$H$_4$→ (structure: O=C, NO$_2$, O=C; HN, NH; HN, NH; O=C, NO$_2$, O=C) —Sn+HCl→ (structure: O=C, NH$_2$, O=C; HN, NH; HN, NH; O=C, NH$_2$, O=C)
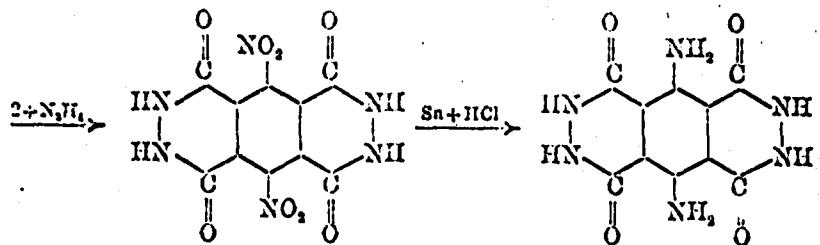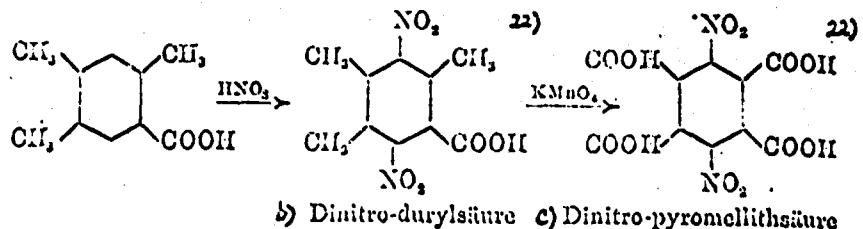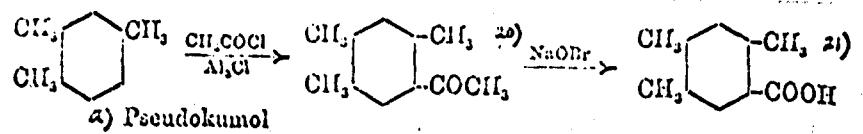
/Legend:_7 a) trimethylbenzene; b) dinitro durylic acid; c) dinitro pyromellithic acid.

Dinitro durylic acid. Nitration was effected without any significant alterations in accordance with the method given by NEF /22_7. Contrary to statements found in reference literature, re-crystallization is easily possible from hot acetone and produces a nicely crstallized compound with a melting point of 203 to 205° C.

The only point that should be kept in mind during this re-crystallization process is to observe proper air drying of the dinitro durylic acid used for this purpose. Also it should be remembered that the acetone in the crystallization liquid should evaporate slowly (at a maximal temperature of 13°C), otherwise oily smear type substances will inevitably be the result. Once the compound has been purified, further re-crystallization from acetone may be accelerated by cautious admixture of petroleum ether (boiling point 70 to 110°C) in cold temperatures.

Dinitro pyromellithic acid. After oxidation by permanganate, a continuous extraction process by means of ether should be used for obtaining a high yield; this will be facilitated by the good solubility of this acid in water. Identical to NEF's results, no clearly defined melting point was obtained: decomposition took place between 209 and 225° Celsius. The acid showed very good solubility in water,

.lcohol and acetone, not in benzol. After repeated re-crystallization from acetone-benzol (1: 10) I obtained a substance with sharply defined melting point and decomposition between 227 and 228° Celsius. An acid anhydride could not be produced since the acid would decompose, during boiling with acetic acid anhydride, under formation of nitric oxides.

Formation of hydrazide. Manufacture of the hydrazide in the usual manner produced a water soluble compound which could only be obtained through extremely slow extraction from ether (in which is latter it is soluble only under difficulty). The compound will dissolve in alkaline solution and will show a violet color. It was possible to re-crystallize this compound from an alcoholic solution under great loss of substance; the result of this procedure was formed by a yellow powder.

2.101 mg substance: 0.294 ccm N (22° C, 763 mm pressure)

$$C_{10}H_4O_3N_4 \quad \text{Computed: } N=25.0 (\%) \quad \text{Found: } N=25.4 (\%)$$

Slight luminescence was observed after addition of hydrogen-peroxyde; a slightly higher intensity was produced by addition of chlorine of lime solution. Melting point: over 260 C, decomposition after 230° C.

Reduction tests with diamine. A yellow compound was obtained by use of stannous hydrochloric acid. This compound was re-crystallized from acetone. When the melting process was observed (after two months) under the microscope, rapid melting was noted at 42° C, sudden re-crystallization occured at 68 to 69° C (producing a new crystalline compound) and no further melting could be recorded until 250° C. No further tests were conducted due to unavailability of material and in view of the fact that the compound had shown only weak luminescence during oxidation.

Substituted Phthalic Hydrazides and Amino-phthalic Hydrazides

Silver salt of phthalic hydrazide. The potassium salt of phthalic hydrazide /23/ is dissolved in water and (under vigorous stirring) combined with the calculated quantity of silver nitrate which causes precipitation of the silver salt in a white form.

4) Benzyl-phthal-hydrazid (I)

- 20 -
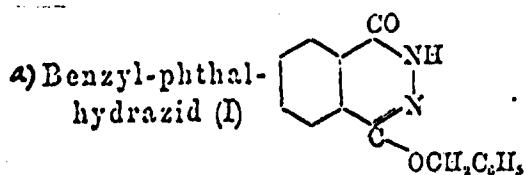
[Legend:] a) Benzyl-phthalic hydrazide (I).

5.2 g of dry, very finely ground silver salt will be
combined with 4 g of benzyl chloride and heated to 130°C for
4 hours. Excessive benzyl chloride will be removed by means
of ? ? . The precipitation will be extracted several times
with ? ?; after concentration to approximately half
? ? the acetone solution is diluted with 1/4
? ? crystallization in the form of white needles will
slowly take place. After re-crystallization with acetone-
water (1:1) the substance will show a melting point of 156°C;
it is not soluble in lye. (A small quantity of a compound
with a melting point of 220°C + was obtained as a byproduct).

?.??? ?? substance: 0.334 ccm N (23°C, 764 mm pressure)

$C_{15}H_{12}O_2N_2$ Computed N=11.11   Found N=11.42

Although the compound is not soluble in diluted sod-
ium lye solution it dissolves (during slight heating) in hy-
drochloric acid of medium concentration, i.e., it has a
slight alkaline character. Benzyl chloride is formed during
heating with concentrated hydrochloric acid which shows the
benzyl group to be present in the molecule in a separable
form. Prolonged heating of the compound beyond its melting
point neither leads to its destruction nor to a transforma-
tion of the hydrazide into its isomeric form.

Mono- and dibenzyl hydrazine (sym.) A mixture of 53
g benzoic aldehyde and 50 ccm methyl alcohol is added to 25
g hydrazine hydrate and 20 ccm methyl alcohol, under constant
stirring and cooling with ice. The solution will remain near-
ly colorless which fact indicates that only a small quantity
of azine has been formed.

The compound thus obtained will be subjected immedi-
ately to hydration by means of Pd-animal-charcoal (0.4 g of
Pd for 9 g of animal charcoal), under 4 atmospheres of pres-
sure. Reduction takes places rather slowly and incompletely.
After approximately 14 hours nearly the computed quantity of
hydrogen will have been absorbed. The filtered solution will
then be subjected to extensive steam (water vapor) distilla-
tion (with hydrochloric acid); the resulting flaky crystal-
line substance may finally be exhausted in cold temperatures.
The compound thus obtained, after final re-crystallization
from hydrochloric alcohol diluted with water, showed a melt-
ing point of 227 to 228° Celsius. It thus represents the
dichloro-hydrate of symmetrical di-benzyl hydrazine which had

previously been produced by another method.

The mother solution obtained in the aforecited manner will be mixed with alkaline solution, extracted by means of ther (in an extraction apparatus) and ben - hydrazine will result from this process, showing a melting point of 113°C.

The benzoic hydrazide obtained showed good sol.... ... ... in the pertinent literature. ... ... dibenzyl-hydrazine was 14 g, in benzyl-hydrazine 15 g. The mono-hydrochloride of benzyl-hydrazine was obtained by feeding hydrochloric acid vapors into an ether solution of hydrazine. The melting point was 112°C. In case of a large exc ss in hydrochloric acid in benzol solution another com..... ....ed which probably represents the di-..... chlor.... ... shows a melting point (not accurately de....ed) of 140°C.

a) Benzyl-phthal-hydrazid (II)
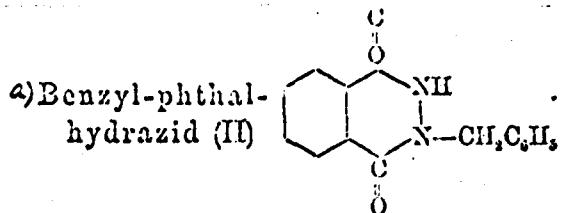
/Legend:/ a) Benzyl-phthalic hydrazide (II).

7 . of phthalic acid anhydride and 6 g benzyl hydrazine are heated in 30 to 35 ccm of absolute ethyl alcohol until complete solution is effected; the alcohol is distilled off and the remaining white crystalline substance is heated to 215°C for 3/4 of an hour. The melt (solidifying during cooling) will be re-crystallized from alcohol. The product will show a melting point of 204°C. Strong depression will occur with phthalic acid. The compound is insoluble in water, as well as in concentrated hydrochloric acid, contrary to its previously described isomeric forms. It is, however, easily soluble in diluted alkaline solution, during slight heating. From this solution it will be precipitated, in unchanged form, by means of acid. As in the case of its isomeric forms, ½ hour of heating the compound beyond its melting point resulted neither in its decomposition nor transformation into one of its possible isomeric forms. Even during extended boiling of the alkaline solution no noteworthy degree of saponification will occur; the latter fact excludes presence of the imide form.

2.8.. mg substance: 0.271 ccm N (23°Celsius, 764 mm pressure)

$C_{15}H_{12}O_2N_2$ Computed N = 11.11   Found N = 11.05

Phthalic acid-dibenzyl-hydrazide I /247/. 3 g of phthalic acid anhydride, combined with 4.2 g of dibenzyl-hydrazine, are heated (for ½ hour) to 165°C in a small open round-bottomed flask. The resulting substance, after re-crystallization from an alcoholic solution, will show a melting point of 153 to 154°C. It solidifies in the form of regularly shaped white crystals and is soluble with difficulty in un-heated alcohol, insoluble in alkaline solution.

2.... .. ..stance: 0.208 ccm N (22°Celsius, 764 mm pressure)

$C_{22}H_{18}O_2N_2$ Computed N=8.19   Found N=8.35

Phthalic acid-dibenzyl-hydrazide II. 3 g of benzyl-phthalic hydrazide (melting point 204°C) will be dissolved in excessive ammonia solution; the excessive ammonia will be expelled from this solution by heating and then the computed quantity of silver nitrate is added. The immediately precipitating silver salt will be filtered off and rinsed thoroughly and repeatedly with water and with boiling alcohol.

1.8 g of this silver salt will then be heated with 1 g of benzyl chloride for ½ of an hour, a small amount of acetone is added and heated for another period at the return flow apparatus. The acetone solution will be poured off (decanted) and the remainder boiled again (several times) with acetone. After evaporation of the combined acetone solutions a white crystalline compound will remain which, after final re-crystallization from water, will show a melting point of 96 to 97°C. This compound, when mixed with the above described hydrazide I, resulted in a marked depression during the melting process.

2.891 mg substance: 0.212 ccm N (23° Celsius, 760 mm pressure)

$C_{22}H_{18}O_2N_2$ Computed N=8.19   Found N=8.46

3-nitro phthalic acid benzyl hydrazide I. 10.6 g of 3-nitro phthalic acid, with 6.1 g of benzyl hydrazine, are heated to 165°C for 2 hours, the temperature is slowly increased to 190 to 200°C and heating is continued at this higher temperature for another 2½ hours. A yellow substance results which, when heated with diluted alkaline solution, showed complete solubility. The substance was dissolved in

a small quantity of diluted alkaline solution, 250 ccm ethyl alcohol and a small quantity of acid solution were added. The resulting viscous compound showed a clearly defined melting point of 212 to 213° C only after repeated re-crystallization from alcoholic solution.

3.420 mg substance: 0.433 ccm N (27° Celsius, 754 mm pressure)

$C_{18}H_{11}O_4N_3$ Computed N=14.14   Found N=14.44

Reduction

The amine is obtained by means of catalytic reduction using Pd-animal charcoal or stannous hydrochloric acid; melting point: 201° C. Melting point increase up to 216° C was noted after re-crystallization from acetone-alcohol solution, melting point reduction (depression) was noted for nitro-benzyl-phthalic hydrazide. Probably a mixture of two isomeric compounds was obtained since continuously changing (not precisely defined) melting points were recorded throughout the various tests conducted. Low but clearly noticeable luminescence was observed with hydrogen peroxyde or hemin used as catalysts.

3.211 mg substance: 0.422 ccm N (24.5° Celsius, 760 mm pressure)

$C_{12}H_{15}O_2N_3$ Computed N=15.73   Found N=15.12(?)

3-nitro-benzyl-phthalic hydrazide II. Obtained from the silver salt by heating with benzyl chloride (analogous to the method previously described for phthalic hydrazide). It was not possible to isolate a pure compound; all attempts yielded a viscous substance containing nitro-phthalic hydrazide.

Nitro-propyl-phthalic hydrazide. 15.7 g of the silver salt of 3-nitro-phthalic hydrazide were heated for 16 hours on the water bath, with 12 g of propylic iodide; 20 ccm of absolute benzol were used as a diluting agent in this process. A strong reaction with generation of heat is observed immediately upon addition of the propylic iodide. The resulting substance was filtered at the end of the reaction and the remainder extracted by means of boiling with acetone. Evaporation of the acetone-benzol mixture left a non-solidifying oil which showed easy solubility in alcohol and hydrochloric acid of medium concentration, but remained insoluble in alkaline solution. It was again dissolved in benzol and rinsed repeatedly in alkaline solution in order to remove possibly remaining traces of nitro-hthalic hydrazide. Despite the insolubility of this compound in alkaline solution, a suspension in

the latter showed luminescence after addition of hydrogen peroxyde. The reduction process with stannous hydrochloric acid yields a greasy substance which could not be purified. Strong and intensive luminescence was observed upon adding of hydrog peroxyde. There is a possibility that traces of the other used had dissociated during the reduction process and formed the cause for the subsequent strong lumine ce.

a repetition of these tests a compound with slight solubility in alkaline solution (3-nitro-phthalic acid-propylic hydrazide) was obtained, with a melting point at 207 to 210°C, which showed the expected composition.

2.381 m substance: 0.421 ccm N (24°Celsius, 760 mm pressure)

$C_{11}H_{11}O_4N_2$ Computed N=16.87   Found N=16.8

Since proper purification from traces of nitro-phthalic hydrazide was impossible due to solubility in alkaline solution, no tests were carried out with this substance. During the same test another product, showing insolubility in alkaline solution, was obtained. This substance showed a mary melting point of 119°C and a clearly defined final ting point of 142°C, after reduction. Further pursuit of ese tests, in particular the difficult separation of isomeric forms, was given up, for the time being, due to the constant change in test results. A conspicuous detail is shown by the fact that the compound with the 142° melting point does not show any signs of luminescence. Since analysis, however, had not given any indication of the presence of the mono-propylic compound but rather showed good coincidence with the specifications of the di-propylic derivate, the complete alkali-insolubility of the nitro compound with the melting point at 109°C would thus be well explained.

3.151 mg substance: 0.434 ccm N (24.5°Celsius, 755 mm pressure)

$C_{14}H_{19}O_2N_3$ Computed N=16.03   Found N=15.91

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